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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,890	11/19/2003	Zhaoning Zhu	IN01535KB	8689

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
SACKEY, EBENEZER O	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,890	ZHU ET AL.	
	Examiner	Art Unit	
	EBENEZER SACKEY	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-57 and 59-72* is/are pending in the application.

4a) Of the above claim(s) *2-57 and 59-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 2-57 and 59-72 are pending.

Claims 1 and 58 have been cancelled.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Response to Restriction

Applicant's election with traverse of Group III, claims 68-72 and species of KX , page 126 of the specification in the reply filed on 04/05/05 is acknowledged. The traversal is on the ground(s) that it is inappropriate to restrict the application into the three groups presented in the restriction. This is not found persuasive because contrary

to applicant's assertion, three distinct Groups or inventions as claimed herein can support their own patents. Each of the specific medical condition embraced in Group (III), is independent from the other since, for example, the treatment of glaucoma is completely different from the treatment of cancer. Hence, the literature search for methods of treating glaucoma would be different as a reference for treating glaucoma would not be in the same reference book as for treating cancer. Furthermore, uses employing compounds and compositions of elected Group III are of a broader scope thus, raising different patentability issues. Similarly, the vast disparity among the various subgroups of formula (I) requires that many divergent fields must be searched, including but not limited to heterocyclic classes 546, 548 etc and non-heterocyclic classes 558 and 562 etc. All of the reasons above constitute an undue burden on the Examiner. Claims 2-57 and 59-67 are withdrawn from further examination as being drawn to non-elected subject matter, 37 CFR 1.142(b)

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art.

See below:

In the instant case, applicants are claiming a method for preventing any and all inflammatory condition or disease.

1) Nature of the invention.

The nature of the invention is methods for preventing inflammatory conditions or diseases, comprising administering the instant compound to a patient in need thereof. As stated, however, claim 68 recites that any or all-inflammatory condition or disease is intended.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between all the diseases claimed as capable of being prevented by compounds of formula (I), one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of inflammation.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would need to determine which of the compounds of the invention would treat all inflammatory condition or disease.

4) Level of predictability in the art.

The art pertaining to the treatment of inflammatory conditions remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art.
Firstly, for a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have

stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is found on pages 24-25 wherein *in vitro* TACE activity is provided. However, that embraces a myriad of inflammatory conditions. In addition, the gap between *in vitro* activity and *in vivo* utility is large enough to warrant thorough and compelling *in vivo* or clinical data.

6) Existence of working examples.

As discussed above, working example is found on pages 24-25 wherein *in vitro* TACE activity is provided. Applicant's limited working example does not enable one of ordinary skill in the art to treat the numerous amounts of diseases encompassed by the instant invention.

7) Breadth of claims.

Claim 68 is extremely broad due to the vast number of possible diseases encompassed by the instant invention.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the treatment of any inflammatory condition or disease. As a result necessitating one of ordinary skill in the art to perform an exhaustive search for which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention. Note:

Genentec Inc. V. *Novo Nordisk A/S* (CAFC) 42 USPQ 2D 1001, states that:

"a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in instant claim, with no assurance of success.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat all, let alone prevent inflammation generally.

This rejection can be overcome by deleting the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid arthritis, osteoarthritis, periodontal disease, cancer and osteoporosis, does not reasonably provide enablement for remaining diseases listed in the claims based solely on inhibition of MMP's receptor functions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. From a reading of the specification, the scope of disorders embraced herein is not enabled as the scope includes **all** MMP receptor functions, which includes diseases very difficult to treat such as autoimmune diseases or cancer. The notion that hydroxamic or carboxylic acid derivatives that are MMP receptor antagonists, the activity relied on herein, have such a range of uses is not seen in the art at the time of applicants' effective filing or even in the present. While MMP receptor blockers are known for treating rheumatoid arthritis, osteoarthritis, periodontal disease, cancer and osteoporosis, there is no evidence of record that there is a correlation of success for the remaining diseases claimed and covered by the instant claims. Note Close, Ann Rheum Dis. 2001, Nov; vol. 60, that Trocade, an

MMP inhibitor did not prevent the progression of joint damage in patients with rheumatoid arthritis. Furthermore, there are at least 26 types of MMP's. An applicant needs to be specific. Also note Greenwald, Annals of New York Academy of Sciences, pages 413-419.

The long list of diseases enumerated constitutes "an invitation to experiment" which is not in compliance with 35 USC 112. See the remarks in Coussens et al., provided herein, Matrix Metalloproteinase Inhibitors and Cancer: Trials and Tribulations, Review: Cancer Therapy, Science Vol. 295, pages 2387-2392 regarding the correlation between MMP's and other diseases. Applicants provide no scientific data in the specification to controvert the findings in the art from which one can reasonably conclude that all of applicant's compounds possess all these uses. Where the assertion of utility is unusual, difficult to treat or speculative, the Examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example, *In re Ruskin,* 148 USPQ 221, *Ex parte Jonanovics,* 221 USPQ 907. Note MPEP. 2164.05(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to E. Sackey whose telephone number is (571) 272-0704. The examiner can normally be reached on Monday-Friday from 7:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272-0699. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

EOS
June 5, 2005

TAOFIQ SOLOLA
PRIMARY EXAMINER

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